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CASE REPORT

Thyrotoxic periodic paralysis: a report of 3 Malaysian cases and a review of its pathology

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Abstract

Thyrotoxic periodic paralysis (TPP) is a medical emergency characterised by sudden onset of muscle weakness with hypokalemia that resolves with the treatment of hyperthyroidism. We report three cases of thyrotoxic periodic paralysis seen at the Accident and Emergency Care Department, University of Malaya Medical Centre in a period of four months. We also review the clinical presentation, pathophysiology, biochemical features and management of TPP. All three patients were young Asian males, presenting with muscle weakness of sudden onset. The first patient presented with lower limb weakness and had symptoms of thyrotoxicosis and goitre. He had a previous similar episode which resolved spontaneously. The second patient presented with quadriplegia, respiratory acidosis and had no signs and symptoms of thyrotoxicosis. The electrocardiogram of this patient showed normal sinus rhythm with U wave in V3 and a flat T wave, which are characteristic of hypokalaemia. The third patient, who was a known case of thyrotoxicosis, was admitted thrice for hypokalemic paralysis during the study period. All cases had low serum potassium, suppressed TSH and elevated T4 confirming thyrotoxic periodic paralysis. Potassium therapy was useful during the crisis; however prophylactic potassium has not been shown to prevent attacks as seen in one of our cases. *Conclusion:* Thyrotoxic periodic paralysis should be considered in the differential diagnosis of sudden onset paralysis in young male patients. Determination of the plasma potassium levels and thyroid hormones help in the diagnosis. The definitive treatment for TPP is the achievement of euthyroid state.

Keywords: Thyrotoxicosis, thyrotoxic periodic paralysis, hypokalaemia.

INTRODUCTION

Hypokalaemic paralysis is a rare cause of acute weakness with a familial predisposition or in association with other diseases. Hyperthyroidism is one of the diverse underlying causes of hypokalaemic paralysis. Thyrotoxic periodic paralysis (TPP) is characterised by hypokalaemia, and progressive symmetrical weakness leading to paralysis of the proximal muscles especially the shoulder and the pelvic girdle. Although the incidence is higher in the Asian population, it has been reported in other ethnic groups. We review the clinical characteristics, pathophysiology, biochemical features and management of three cases of TPP presenting at the Accident and Emergency Care Department (A/E), University of Malaya Medical Centre (UMMC) in a period of four months (September 2002 to December 2002).

CASE REPORTS

Case 1

A 21-year-old Chinese male, university student presented at dawn to the Emergency Department with sudden onset of lower limb weakness, and inability to walk after he awoke from sleep. He had a similar episode the previous day, which resolved spontaneously after an hour. His vital signs were blood pressure 110/70 mmHg; pulse 100 beats per minute and respiratory rate 18 breaths per minute.

Clinically, he had a diffusely enlarged goitre with bruit. His hands were warm and moist with fine tremor and no exophthalmos. On neurological examination, the strength of the proximal muscles in both the lower limbs was graded as 1/5 with reduced deep tendon reflexes. There was no impairment of sensory function;

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cranial nerves were normal and there was no incontinence of urine or faeces. Initial electrolyte analysis showed the potassium level to be 2.4 mmol/L. Other electrolytes, urea, creatinine and glucose were within the reference range. The levels of calcium, magnesium, and phosphate were normal. The free T4 was found to be elevated (92.3 pmol/L) and TSH was low (< 0.02 uIU/ml), thereby confirming the diagnosis of hypokalaemia due to thyrotoxicosis.

Case 2

A 36-year-old Thai male, a construction worker, presented to the Emergency Department at 2 am with weakness of the lower limbs and severe shoulder pain of sudden onset. Clinically, the patient was alert, conscious and cranial nerves were intact. There was no stridor and no urinary or faecal incontinence. Vital signs were normal. Neurological examination revealed marked muscle weakness of the proximal muscles in both lower and upper limbs, reduced deep tendon reflexes but with no sensory loss. There were no signs and symptoms suggestive of thyrotoxicosis. However, the laboratory data indicated that the patient had marked hypokalaemia (1.8 mmo/L) and increased level of creatine kinase (381 IU/L). The ECG showed normal sinus rhythm and U wave in V3 and a flat T wave. The arterial blood gas analysis indicated respiratory acidosis. Thyroid function test (free T4-66.8 pmol/L and TSH < 0.02 uIU/ml) confirmed that the patient was hyperthyroid. All the other biochemical investigations were unremarkable.

Case 3

A 27-year-old Malay male presented to the A/E department with weakness of the lower limbs. He was a known case of thyrotoxicosis and was on treatment for the same. He had obvious signs and symptoms and a family history of thyrotoxicosis. During the study period, he was admitted on three occasions to the hospital with a similar complaint. His potassium levels during his admissions were noted to be low (2.2, 2.4 and 2.7 mmol/L respectively) and free T4 levels were 59.3, 45.8 and 42.6 pmol/L and TSH was <0.02 uIU/L, thereby confirming that he had TPP during his three admissions.

Treatment

All 3 patients were treated with intravenous potassium. Once the potassium levels were normalised, they were started on oral potassium replacement therapy and were discharged within three days of admission with anti-thyroid drugs.

DISCUSSION

Hypokalaemic paralysis represents a heterogeneous group of disorders with a common clinical presentation - acute weakness or paralysis affecting the neuromuscular system. The causes include "familial hypokalaemic paralysis," thyrotoxic periodic paralysis, renal tubular acidosis, barium poisoning, primary aldosteronism and gastro-intestinal potassium losses. The approach to the diagnosis of patients with hypokalaemic paralysis includes a vigorous search for the underlying aetiology and the management is potassium replacement therapy as well as treatment of the underlying condition.

Clinical presentation

Thyrotoxic hypokalemic paralysis is a rare complication of thyrotoxicosis. Rosenfeld first described the link between hyperthyroidism and periodic paralysis in 1902. Although the incidence of TPP is reported to be higher among Asians, it has been reported in other ethnic groups.[1] While thyrotoxicosis affects females predominantly, the incidence of TPP is more common in males. The age of onset is usually in the 3rd to 5th decades of life. Paralysis tends to occur on awakening, after exercise or following consumption of a high carbohydrate meal.[2]

The flaccid paralysis is more prominent in the lower extremities than in the upper limbs[3] and is usually bilateral. Proximal muscles are affected more often than the distal muscle groups and the same clinical presentation was observed in all our 3 cases. Rarely, the presentations could be similar to that of upper motor neuron disorder or respiratory dysfunction.[4,5] Sensory function is not altered in TPP. Deep tendon reflexes can be diminished or absent; reduced deep tendon reflex was noted in two of the cases. In one of the patients, respiratory acidosis was diagnosed by arterial blood gas analysis and this indicated weakness of the respiratory muscles.

The main biochemical abnormalities during the paralysis are high levels of thyroid hormones and hypokalaemia. The hypokalaemia is not due to depletion of the body potassium but due to intracellular shift of the potassium.[6] Apart from hypokalaemia, hypophosphataemia has been reported during an attack of TPP.[7] Hypophosphataemia could also be explained by an intracellular shift of phosphate.[7] Upon resolution of paralysis, the phosphate level

returns to normal. We did not observe any decrease in phosphate levels in any of our cases.

Electrocardiograph manifestations may include typical features of hypokalaemia; this includes U waves (in leads V2 to V4), flattened T waves, and QT prolongation.[8] Apart from this, disturbances in rate and rhythm may occur including sinus tachycardia, atrial flutter, atrial fibrillation, atrial and ventricular extra-systoles and rarely ventricular fibrillation.[9]

The factors that precipitate TPP attack include ingestion of a high carbohydrate diet and strenuous exercise followed by rest.[2] Attacks can also be precipitated by alcohol ingestion, emotional stress and medications such as diuretics and insulin.[3] The attacks are noted to have a seasonal incidence, occurring more commonly in warmer months compared to colder months.[2]

Pathophysiology

The mechanism of TPP remains unclear. It is probably due to increased activity of Na-K-ATPase.[10,11] It has been shown that excessive thyroid hormones can induce increased permeability of the muscle membrane to electrolytes, with influx potassium into cells associated with failure in depolarisation.

The aetiological factors associated with hypokalaemic paralysis in TPP patients include hyperthyroidism,[11] genetic and racial predisposition, exaggerated insulin response,[12] hyper-adrenergic state,[13] and probably other mechanisms leading to intracellular shift of potassium and phosphate. Studies have shown that insulin response to meals is markedly higher in the evening compared to the response in the morning.[14] This may possibly explain the nocturnal preponderance of TPP.

Genetics

Periodic paralysis, without a familial background, manifests only in the thyrotoxic patient. A study of HLA haplotypes in Japanese men with TPP, suggested that the HLA-DRW8 gene itself may play a significant role in the susceptibility of TPP.[15] In another study, HLA antigens A2BW22 and AW19B17 were found in Chinese patients.[16] In black men, neither of these haplotypes has been observed. Although the HLA system has been suggested to provide a link to an immunogenic aetiology, it seems to be an unlikely explanation because in patients with TPP, thyrotoxicosis need not be due to an autoimmune mechanism.

The first genetic defect in TPP was identified by Dias Da Silva *et al.* A mutation was found in KCNE3, the potassium ionic channel gene.[17] They identified the R83H mutation in KCNE3 gene, the potassium ionic channel gene. It is clear that more studies are required to identify the basic genetic defect that is responsible for TPP in thyrotoxic patients and to delineate the mechanism underlying hypokalaemic paralysis.

Treatment

The treatment of TPP is administration of potassium to hasten the recovery of the paralysis and to avoid the associated cardiac complications of hypokalemia. In TPP, total body potassium levels are unaltered, unlike that of FHP, and hence aggressive potassium therapy may cause a "rebound" hyperkalaemia. Lin SH, *et al.* used propranolol to reverse paralysis, hypokalemia and hypophosphataemia. Propranolol down-regulates Na-K-ATPase activity.[18] Generally, patients are prescribed oral supplemental potassium to avoid recurrence of the paralysis. However, it has been proven to be ineffective in the prevention of recurrence,[19] a finding we observed in one of our patients. In some cases, spironolactone is used to prevent the paralysis.[2] Both spironolactone and beta adrenergic blockers have been reported to reduce the frequency of attacks.[2] This may be an effective treatment while waiting for the patient to achieve euthyroid status.

The definitive therapy for TPP is the achievement of euthyroid state by medical, surgery or radioactive iodine therapy. The resolution of periodic paralysis occurs with the restoration of euthyroidism. After initiating the definitive treatment for thyrotoxicosis, patients should be advised to avoid the known precipitating factors.

CONCLUSION

Thyrotoxic periodic paralysis should be considered as one of the differential diagnosis when Asian males present with muscle weakness soon after awakening. Hypokalemia is the most consistent electrolyte abnormality in TPP. Although the pathogenesis of this condition is still not clear, there is strong evidence that complete resolution occurs following successful treatment of the thyroid dysfunction. Therefore, it is imperative that the attending physician recognises the characteristic clinical features of TPP and distinguishes it from other similar forms of paresis. The definitive treatment is to

treat the thyrotoxicosis. Propranolol and spironolactone can be used to prevent the paralytic attacks. Oral supplemental potassium is not effective in preventing the relapse. Potassium is useful mainly to hasten the recovery and prevent cardiac arrhythmias during the attack.

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